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Among the drugs used for treatment of psychoses are those compounds which have a degree of anticholinergic action directly on eccrine sweat glands which disrupts thermoregulation. Atropine (a potent nerve agent antidote) reduces thermoregulatory sweating causing intense heat storage often leading to hyperpyrexia. A heat exchange analysis was carried out using a database of previous studies in our Institute in which saline and atropine (2 mg im) were injected in 14 healthy male subjects before and after heat acclimation. Subjects walked on a treadmill in hot-dry and hot-wet environments.
A new effective temperature (ET*) was generated that can be implemented in any heat exchange evaluation utilizing biophysical and physiological data including mean skin temperature, rectal temperature, heart rate, metabolic activity, and skin evaporative heat loss. Heat acclimation reduced ET* by some 2.5°C when compared with the unacclimated state after atropine injection. Heat acclimation thereby potentially lessens the hazards of heatstroke caused by exercise in the heat with atropine injection. Such a heat exchange model can be used to predict responses to other anticholinergic agents and has potential relevance applied in understanding psychotropic drug-related hyperthermia.

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Prediction of anticholinergic drug response using a thermoregulatory exchange index

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Abstract

1. Among the drugs used for treatment of psychoses are those compounds which have a degree of anticholinergic action directly on eccrine sweat glands which disrupts thermoregulation. Atropine (a potent nerve agent antidote) reduces thermoregulatory sweating causing intense heat storage often leading to hyperpyrexia.
2. A heat exchange analysis was carried out using a database of previous studies in our Institute in which saline and atropine (2 mg i.m.) were injected in 14 healthy male subjects before and after heat acclimation. Subjects walked on a treadmill in hot-dry and hot-wet environments.
3. A new effective temperature (ET*) was generated that can be implemented in any heat exchange evaluation utilizing biophysical and physiological data including mean skin temperature, rectal temperature, heart rate, metabolic activity, and skin evaporative heat loss.
4. Heat acclimation reduced ET* by some 2.5°C when compared with the unacclimated state after atropine injection. Heat acclimation thereby potentially lessens the hazards of heatstroke caused by exercise in the heat with atropine injection.
5. Such a heat exchange model can be used to predict responses to other anticholinergic agents and has potential relevance applied in understanding psychotropic drug-related hyperthermia.

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Keywords: Heat acclimation; Anticholinergics; Hyperthermia

1. Introduction

The advent of antipsychotic drugs (Bark, 1982) also brought about compounds known to impair thermoregulation (Brown and Mann, 1985; Haraguchi et al., 1997). Many of the drugs used for treatment of psychoses include compounds which are anticholinergic. These include phenothiazines, butyrophenones (haloperidol) and others used to combat Parkinsonism. The weakest of these, haloperidol, and the strongest, atropine, severely alter sweat gland secretion often causing a drastic reduction in sweating and, therefore, reduced evaporative cooling. The thermoregulatory mechanisms allowing healthy, heat-acclimated or exercise-trained individuals to compensate for lack of sweating may be poorly developed in psychiatric patients (Bullard et al., 1970; Kolka et al., 1984).

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One contributor to the decreased homeostatic compensation in such individuals chronically taking a specific drug is possibly poor physical fitness. Physical fitness may be characterized by maximum aerobic power or some other fitness criterion (Davies et al., 1978). Other factors predisposing thermoregulatory dysfunction include age, poor nutrition (and consequent low immune response) and obesity. When challenged exogenously by environmental heat stress, or endogenously via fever or exercise, a person's facility to maintain body heat balance is the critical means to dispel heat. If a person is not storing heat and internal body temperature is constant, then the person is said to be in thermal equilibrium with the environment. The rate of heat produced by metabolism (M) is equal to the rate of heat loss by thermal radiation (R), convection and conduction (C) and evaporation (E_{sk}).

E_{sk} occurs when water is dispelled by the respiratory tract or through the skin and evaporates into the air. Effective regulation of skin blood flow (SkBF) allows the body to control the amount of $R + C$ transferred from the core to the body surface and to the environment (Gagge and Gonzalez, 1996).

The thermoregulatory system in humans is unique in certain aspects in guarding against both hypothermia and hyperthermia. The processes regulating metabolism and increasing or decreasing peripheral blood flow also actively participate in control of other regulatory central mechanisms such as the endocrine, circulatory and respiratory systems. The sudomotor system, on the other hand, has evolved exclusively as a dedicated process to guard against hyperthermia (Boulant, 1996; Bullard et al., 1970). Minimal, if any, interfacing signals alter the output (effector) response from a central nervous drive to the individual sweat gland. Thus, the change in sweat gland pattern and its magnitude over time becomes a reliable method to demonstrate degree of potentiation or dysfunction of a thermal response. These sweating responses allow the deduction of general characteristics of thermoregulation with some confidence that there are minimal interferences from other regulatory systems (Hammel, 1965). The techniques and interpretations derived from sweating responses in healthy persons can, generally, be applied to studies in patients exposed to anticholinergics and other drug treatment.

This paper reports on a database of past studies (Kolka et al., 1984, 1986, 1994) carried out in our Institute using fit subjects in which thermoregulatory responses were studied following atropine injection. *Study A* addressed the overall effects of heat acclimation during steady-state exercise. *Study B* examined the effects of dry heat exchange during exercise in warm-humid and warm-dry environments in heat-acclimated persons. A new effective temperature (ET*) was generated that can be incorporated into the heat balance equation for any environment and may be applicable to the analysis of drug efficacy.

2. Methods

2.1. Study A

Eight males volunteered for this study following consent procedures passed by the US Army Human Use Review Committee. The subjects had an average ($\pm$SD) age of 22 ± 3 year, weight of 79.9 ± 9.8 kg, Dubois surface area (m^2) of 2.02 ± 0.16, and % body fat (hydrostatic weighing method) of $14.6\% \pm 4.6\%$; maximum aerobic power ($VO2$ max) of the subjects was 50.2 ± 6 ml kg^{-1} min^{-1}. Testing occurred in a large tropic/wind chamber during March–May. All subjects were tested with the drug injection prior to heat acclimation (Kolka et al., 1984) and then after a period of 10 days of heat exposure. Heat acclimation (49°C/20%rh, $P_a = 17.6$ Torr, 2.35 kPa) was confirmed when rectal temperature and/or heart rate had levelled off. All eight subjects walked on a treadmill set at 1.34 m s^{-1} (metabolic rate of 180 W m^{-2}). The subjects were in good health and had not taken any prescribed or unprescribed medication or alcohol during the course of the experiments.

Each subject completed an exercise-heat exposure twice during each pre-acclimation period. On one occasion, 2 mg of atropine sulphate (Elkin-Sinn, Cherry Hill, NJ) was injected into the vastis lateralis immediately before the subjects entered the environmental chamber (15 min before the onset of exercise). The second pre-acclimation exposure involved the intramuscular (i.m.) injection of an identical volume of sterile saline. These exposures were randomized and separated by at least 2 days to avoid possible carry-over effects of acute heat exposure. The post-acclimation testing was identical to the pre-acclimation testing: once after the i.m. injection of atropine sulfate and again after the i.m. injection of sterile saline. These exposures were randomized and separated by one day. The testing consisted of an exercise-heat exposure (25% $VO2$ max, $T_a = 49°C$, rh = 20%) in which the subjects, dressed in gym shorts and athletic shoes, attempted to walk (1.34 m s^{-1}) on a level for repeated bouts of 10 min rest, 25 min exercise until voluntary termination or 140 min elapsed. Rectal (T_{re}), mean skin temperature ($\bar{T}_{sk}$), and heart rate were continuously monitored. Metabolic heat production was calculated by open-circuit spirometry. Total body sweating rates were determined from body weight changes, each 25 min utilizing a precision balance (± 0.005 kg).
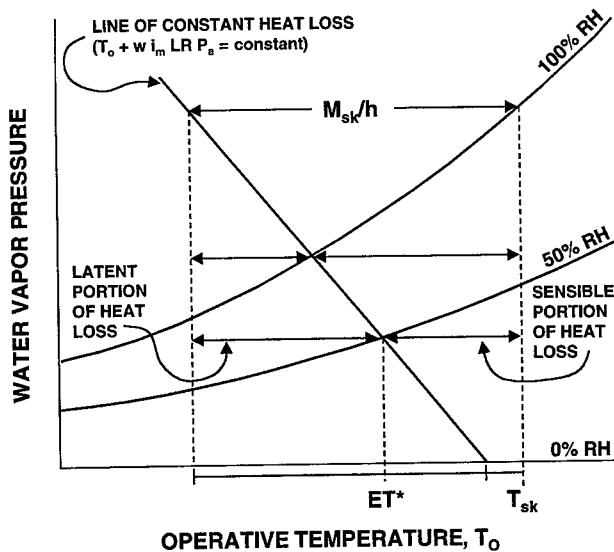
Fig. 1. Expression of sensible and latent heat losses in terms of water vapor pressure (*y*-axis) and operative temperature (*x*-axis) on a psychrometric graph. Operative temperature (T_o) is defined as the average of T_a and mean radiant temperature, weighted by respective convective and radiative heat transfer coefficients. Effective temperature (ET*) is determined by vertical intersection of operative temperature with the 50% rh line.

2.2. Study B

Six new subjects, independent of Study A, were exposed two times at each environmental condition. The environmental conditions were as follows.

1. Warm/dry, globe temperature (T_g) of 41°C, ambient water vapor pressure ($P_a = 12$ Torr, 1.6 kPa).
2. Moderate, $T_g = 35$°C, $P_a = 22$ Torr, 2.93 kPa.
3. Humid: $T_g = 32$°C, $P_a = 22$ Torr, 2.93 kPa (Kolka et al., 1994).

The latter two environments were chosen to facilitate insensible heat loss and yet be in the zone where skin blood flow can still affect skin surface temperature by modulation of vasoconstrictor outflow.

Two mg of atropine sulfate (1 ml) were injected into the subject's vastis lateralis muscle 10 min prior to the beginning of the exercise-heat exposure. In separate experiments, 1 ml of saline was injected prior to heat exposure. The order of injections of atropine and saline was counterbalanced over the subjects. The atropine trials were separated by at least four days with no testing.

The exercise level was 25% $\dot{V}O2$ max, as in Study A, set by a level motor-driven treadmill (1.34 m s^{-1}). However, exposure time was continuous for a period of 100 min or until rectal temperature (T_{re}, °C) exceeded 39.5°C, heart rate (HR, b min^{-1}) exceeded

180 b/min for 5 min, or the subject voluntarily decided to terminate the experiment. As in Study A, T_{re}, $\bar{T}_{sk}$, and HR were recorded. Metabolic heat production (M, W m^{-2}) was calculated from $\dot{V}O2$ at min 30, 60, and 90 min using open circuit techniques. Total body sweating rates (g min^{-1}) were determined by pre- and post-exercise weighings.

3. Results

3.1. Study A

A partitional calorimetric analysis (Gagge and Gonzalez, 1996) was done incorporating all environmental and physiological variables following 30 min post-injection in subjects completing a full exercise bout. The heat balance was then described in a graphical format in terms of two independent gradients with the *y*-axis depicting ambient vapor pressure (P_a) and the *x*-axis showing operative temperature (T_o).

Fig. 1 depicts graphically each avenue of heat exchange requiring only an accurate measurement of convective, radiative and evaporative heat transfer coefficients and knowledge of net heat flow (M_{sk}) through the skin surface. M_{sk} may be determined from metabolism (M), less work level (Wk), less evaporative (E_{sk}), respired (E_{res}) and convective (C_{res}) heat losses (all in W m^{-2}). This relationship is shown analytically in Eq. (1) for thermal equilibrium conditions in unclothed persons as:

$$(P_a - P_{s,\,sk}) = -(h/wh_e)[T_o - (\bar{T}_{sk} - M_{sk}/h)]$$

$$\text{[Torr or kPa]} \tag{1}$$

The ratio (h/h_e) is the combined physical heat transfer characteristic of the environment describing extent of sensible (non-evaporative) to latent (e.g., insensible) heat exchange in any environment. For the clothed state (including protective clothing), the transfer constant is determined by incorporation of clothing coefficients differentiated for dry heat and latent heat transfer (Gagge and Gonzalez, 1996). $P_{s,sk}$ is the skin saturation vapor pressure (Torr) and w is the skin wettedness, the fraction of the skin surface that is wet with sweat determined by a ratio of evaporative heat loss (E_{sk}) to maximum evaporation possible (E_{max}). Fig. 2 shows how specific physiological variables change following the anticholinergic response on the psychrometric chart as heat balance properties change. Any of the dependent physiological variables governing heat exchange such as ($\bar{T}_{sk}$), skin wettedness (w) due to regulatory sweating, internal body temperature or skin blood flow (SkBF) are easily displayed. The relationship ($\bar{T}_{sk} - M_{sk}/h$) in Eq. (1) may be described in
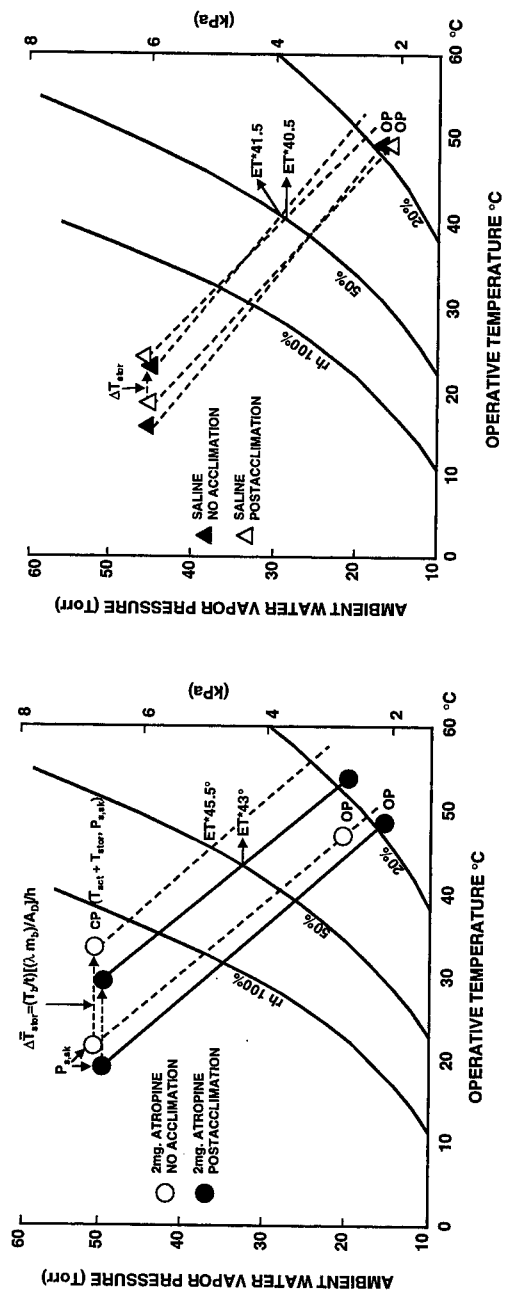
Fig. 2. Effect of 2 mg atropine (left panel) and saline injections (right panel) on the rate of heat storage ($\Delta \bar{T}_{stor}$) expressed on the psychrometric graph. ET^* is lower following the atropine injection in the heat acclimated state. OP is the operating point (°C) of the environmental stress experiments and CP is the common point based on the x, y coordinates of $T_{act} + T_{stor}$ (°C) and skin saturation vapor pressure for each OP. Redrawn from Kolka et al. (1986).

terms of a single temperature (T_{act}) which is associated with internal body temperature rise as sweat glands become inhibited by atropine (or any other drug inhibiting sudomotor activity). Maximum inhibition (leading to increased heat storage and potential hyperpyrexia) theoretically should occur when plasma levels of a given drug are at their highest (ca. 20 min for atropine) (Metcalf, 1981). Each displacement during any transient changes in heat balance (Fig. 2) becomes apparent on the right axis of operative temperature and signifies the combined outcome of sensible heat exchange plus rate of heat storage ($T_{act} + T_{stor}$) as

$$T_{stor} = (\bar{T}_b/t)[(\lambda m_b)/A_D]/h \quad [C] \qquad (2)$$

where λ is the specific heat constant (W h kg^{-1} °C^{-1}) and m_b is body mass (kg) and A_D is Dubois surface area (m^2). The combined heat transfer coefficient (h) includes appropriate evaporative, radiative, and convective heat transfer coefficients determined for both unclothed and clothed individuals from classical heat exchange equations (Gagge and Gonzalez, 1996).

An effective temperature index (ET*), which assesses both dry heat stress and humid heat stress in terms of observed heat exchange derived from Eq. (1) has been shown to match physiological strain consistently over wide exercise intensities (Gagge and Gonzalez, 1996). This ET* is defined as the dry bulb temperature (T_a) at 50% rh in which total heat exchange from the skin surface is T_a and P_a. Fig. 2 shows ET* graphically defined by operative temperature, T_o (on the x-axis). ET* is a useful index for predicting efficacy of heat acclimation (Kolka et al., 1984) in modulating the effects of atropine (or any drug that alters heat storage) on specific sweat glands at a given time of exposure. ET* is a rationally-determined temperature index of an isothermal enclosure (T_a = operative temperature, T_o) comparable to a surrounding ambient in which a person would exchange the same total heat by sensible heat ($R + C$) and latent heat loss by E_{sk} (Fig. 1). ET* is analytically determined by

$$ET^* = T_o + wi_m LR(P_a - 0.5P_{s,\,ET^*}), \quad [C] \qquad (3)$$

where P_{s,ET^*} is the saturated vapor pressure at ET*, i_m is the Woodcock vapor permeation coefficient for clothing resistance, and LR is the Lewis relation applied to sea level environments (2.2°C/Torr or 16.5°C/kPa) (Gagge and Gonzalez, 1996). ET* conveniently quantifies the summed effect of the environmental heat stress and strain that a person can apply to describe thermal "sensation" to the surrounding micro-environment. Any higher level from a given threshold in ET* can be immediately determined by showing impairments in heat exchange as a consequence of an anticholinergic drug. The efficacy of a given drug causing a change in the operating point from a physiologically neutral level (by changes in T_{act}) may be potentially ranked by these changes and the ET* becomes a useful descriptor of drug interaction on heat exchange properties.

Fig. 2 shows that heat acclimation per se lowers the ET* (intersection of 50% rh line) by some 1°C in comparison to the unacclimated state after saline challenge. In the heat acclimated state, however, ET* became reduced (e.g., what a person's physiological system "senses") by some 2.5°C compared to unacclimated state following atropine injection.

3.2. Study B

In the above previous study it is obvious that after atropine, markedly decreased skin sweating levels were observed compared to the experiments observed with saline injection. Potentiation of dry non-evaporative heat loss (by $R + C$) following heat acclimation, required to dispel metabolic heat during exercise, would have to occur to result in a smaller T_{stor}. The heat acclimated state allows a more efficient dumping of metabolic heat by the peripheral circulation (Kolka et al., 1994). In Study B, the effects of atropine injection on the T_{re} responses in terms of ET* were examined during exercise in the heat on six men completing 54 min of exercise at three discrete environments. At environments of ET* = 37.7°, 35.5° and 35.3°C, final mean T_{re} for the atropine-injected group were 38.6°C, 38.2°C and 37.8°C, respectively. All were different from each other ($p < 0.05$). Control experiments following saline injection displayed a mean T_{re} of 37.5 ± 0.15°C, 37.5 ± 0.13°C and 37.4 ± 0.16°C, (NS) for each of the above ET*s. The increments in T_{re} between the atropinized subjects and the saline-injected subjects were significantly different ($p < 0.05$).

4. Discussion

Bark (1982) reviewed the literature dealing with heatstroke in psychiatric patients. A higher incidence of heatstroke was evident in patients taking antipsychotic drugs with anticholinergic properties (mepazine, chlorpromazine, thorazine) (four deaths: 10 cases). Interestingly, even drugs such as haloperidol (popular as an anti-anxiety drug), with purported minimal anticholinergic effects, were associated with heatstroke cases when combined with antiparkinsonian drugs. It is also possible that drugs with anticholinergic properties may induce catalepsy as well and this becomes exacerbated in the heat by synergy with various neuroleptics (Haraguchi et al., 1997). Clearly, it is apparent that residual anticholinergic medication in patients affects their physiologic responses in several ways. One way

may be associated with level of thermoregulatory incompetence to resist hyperthermia. To a great extent this inability is often due to the patient's lack of heat acclimatization, physical fitness, and other complicating properties (hypo-hydration, time of day, etc). Although our heat exchange analysis is limited to healthy subjects, it shows that as a practical application, any hazard of heat stroke caused by work-in-the-heat routines following anticholinergic drug application may be effectively diminished by heat acclimation (Kolka et al., 1984). Heat acclimation also has the consequent effect of reducing the effective temperature (ET*). ET*, in turn, appears to be a robust dynamic index useful in modeling responses that is uniquely tied in with a person's metabolic activity, body core temperature, clothing worn, mean skin temperature, and evaporative heat loss (Gagge and Gonzalez, 1996).

Isolated sweat glands from heat-acclimated or well-trained persons have been found to be more sensitive to methacholine, have a higher secretory rate per unit tubule length, and are larger than that found in untrained individuals (Sato and Sato, 1981). Such adaptations demonstrate a higher cholinergic sensitivity (Bullard et al., 1970; Hammel, 1965). Heat acclimation has been shown repeatedly to induce an augmented efferent drive to the sweat gland which results in a greater liberation of acetycholine or indeed, allows more receptors to become available which are not blocked by the same dosage given to unacclimated individuals (Davies et al., 1978; Haraguchi et al., 1997). Subsequently, any potentiation of sensible (dry, non-evaporative) heat loss by heat acclimation or a greater thermal sensitivity of the responses of skin blood flow plotted against core temperature increases could occur which would offset any imbalances in evaporative heat loss (Kolka et al., 1994). Some evidence using an animal model indicates that preoptic/anterior hypothalamic dopaminergic synapses may function to counter hyperthermia by either facilitating heat loss (skin blood flow) or inhibiting heat production responses (Boulant, 1996).

Characteristically, sustained light to moderate exercise is accompanied by an increase in body temperature which remains elevated for the duration of the exercise period. This endogenous (and reversible) hyperthermia results from the fact that heat production is greater than heat loss causing a higher rate of body heat storage (Gagge and Gonzalez, 1996). The less one is acclimatized to heat, the greater the risk of hyperthermia during physical work at increased ambient temperature (Davies et al., 1978). In the studies examined here, subjects were in excellent physical condition yet T_{re} increased by some 1.4°C. It is a common observation that the physical status with respect to "conditioning" or "fitness" (described by a maximum

aerobic power) is poor in the majority of psychiatric patients taking medication with some anticholinergic activity. This situation, combined with psychotropic medication could further predispose such individuals to the risk of hyperthermia.

Another factor that can influence the hyperthermic response includes age. It is now generally accepted that the incidence of adverse reactions to drugs increases with the age of the patient (Bark, 1982; Brown and Mann, 1985), but more precise reasons are obscure. One cause may be attributed to a longer biological half-life of many drugs in the elderly combined with alterations in tissue responsivity to drug action (Metcalf, 1981). The incidence of heatstroke being greater in older people thus would place such a psychiatric patient population at double risk.

In summary, heat acclimation improves the heat tolerance of persons under the influence of atropine by reducing the effective temperature (ET*). Heat acclimation also allows compensation by dry heat exchange and subsequent improved skin blood flow during reduction in sweating rate due to anticholinergic action. The thermoregulatory exchange index as developed here, which has physiological framework rather than a sensory basis, could be readily applied in any epidemiological screening to predict heat strain in patients using a variety of antipsychotic drugs having anticholinergic tendencies.

The views, opinions and/or findings in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other official documentation. Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to US Army Medical Research and Materiel Command Regulation (70-25) on Use of Volunteers in Research. Citation of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or service of the organizations. Approved for public release; distribution is unlimited.

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